

**Version With Markings To Show Changes Made**

**Amendments in the Specification:**

In accordance with 37 CFR 1.121(b), the following paragraphs of the specification as rewritten by the foregoing amendments show all changes made relative to the previous version of the paragraphs.

Please rewrite page 1, paragraph 2, as follows:

Cell mitosis is a multi-step process that includes cell division and replication (Alberts, B. et al. In *The Cell*, pp. 652-661 (1989); Stryer, E. *Biochemistry* (1988)). Mitosis is characterized by the intracellular movement and segregation of organelles, including mitotic spinkles and chromosomes. Organelle movement and segregation are facilitated by the polymerization of the cell protein tubulin. Microtubules are formed from  $\alpha$  and  $\beta$  tubulin polymerization and the hydrolysis of [GTP] guanosine triphosphate (GTP). Microtubule formation is important for cell mitosis, cell locomotion, and the movement of highly specialized cell structures such as cilia and flagella.

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Please rewrite page 2, last paragraph, as follows:

I have discovered that certain compounds within the scope of the general formulae set forth below in the claims are useful for treating mammalian diseases characterized by undesired cell mitosis. Without wishing to bind myself to any particular theory, such compounds generally inhibit [microtubule] microtubule formation and tubulin polymerization and/or depolymerization. Compounds within the general formulae having said inhibiting activity are preferred. Preferred compositions may also exhibit a change (increase or decrease) in estrogen receptor binding, improved absorption, transport (e.g. through blood-brain barrier and cellular

membranes), biological stability, or decreased toxicity. I have also discovered certain compounds useful in the method, as described by the general formulae of the claims.

Please rewrite page 3, second full paragraph, as follows:

[The bond indicated by C• •C is absent or, in combination with the C---C bond is the unit HC=CH.]

Please rewrite page 3, line 29, as follows:

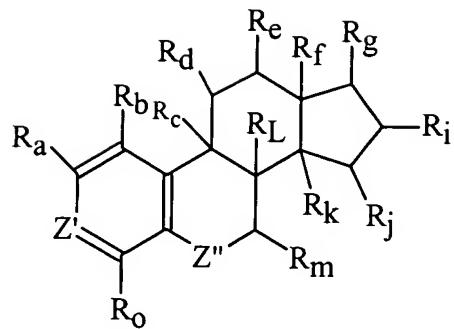
[Description of the Preferred Embodiments] BRIEF DESCRIPTION OF THE DRAWING

Please rewrite page 3, paragraph 4, as follows:

[The drawings are first described.]

Please rewrite page 4, third paragraph, as follows:

As described below, compounds that are useful in accordance with the invention include novel estradiol derivatives that bind tubulin, inhibit microtubule formation or exhibit anti-mitotic properties. Specific compounds according to the invention are described below.



wherein:

I.  $R_a$ - $R_o$  are defined as follows:

A) each  $R_a$ ,  $R_b$ ,  $R_c$ ,  $R_d$ ,  $R_e$ ,  $R_f$ ,  $R_i$ ,  $R_j$ ,  $R_k$ ,  $RL$ ,  $R_m$ ,  $R_o$ ,

independently is  $-R_1$ ,  $-OR_1$ ,  $-OCOR_1$ ,  $-SR_1$ ,  $-F$ ,  $-NHR_2$ ,  $-Br$ , or  $-I$ ; and  $R_g$  is  $-R_1$ ,

$-OR_1$ ,  $-OCOR_1$ ,  $-SR_1$ ,  $-F$ ,  $-NHR_2$ ,  $-Br$ ,  $-I$ , or  $-C\equiv CH$ ;

or

B) each  $R_a$ ,  $R_b$ ,  $R_c$ ,  $R_f$ ,  $R_k$ ,  $RL$ ,  $R_o$ , independently is  $-R_1$ ,  $-OR_1$ ,  
 $-OCOR_1$ ,  $-SR_1$ ,  $-F$ ,  $-NHR_2$ ,  $-Br$ , or  $-I$ ; and each  $R_d$ ,  $R_e$ ,  $R_i$ ,  $R_j$ ,  $R_m$ , independently is  $=O$ ,  $-R_1$ ,  $-OR_1$ ,  $-OCOR_1$ ,  $-SR_1$ ,  $-F$ ,  $NHR_2$ ,  $-Br$  or  $-I$ ; and  $R_g$  is  $=O$ ,  $-R_1$ ,  $-OR_1$ ,  
 $-OCOR_1$ ,  $-SR_1$ ,  $-F$ ,  $-NHR_2$ ,  $-Br$ ,  $-I$ , or  $-C\equiv CH$ ;

and

II.  $Z'$  is defined as follows:

A)  $Z'$  is  $X$ , where  $X$  is  $>COR_1$ ,  $>CC-R_1$ ,  $>CC-OR_1$ ,

$\begin{array}{c} OH \\ | \\ >CCH-R_1 \end{array}$  or  $\begin{array}{c} OH \\ | \\ >CCH-OR_1 \end{array}$ ;

or

B)  $Z'$  is  $=C-X'-$  or  $-X'-C=$ ,  
 $\begin{array}{c} | \\ R_n \end{array}$        $\begin{array}{c} | \\ R_n \end{array}$   
where  $R_n$  is  $-R_1$ ,  $-OR_1$ ,  $-SR_1$ ,  $-F$ ,  $-NHR_2$ ,  $-Br$  or  $-I$ ;

and  $X'$  is  $X$ , as defined above; or  $X'$  is  $>C=O$ ;

and

III.  $Z''$  is defined as follows:

A)  $Z''$  is  $Y$ , where  $Y$  is  $-O-$ ,  $-N-$ ,  $>CHR_1$ ,  $>C=O$ ,  
 $\begin{array}{c} R_1 \\ | \\ >C-(CH_2)_nOR_2, \end{array}$

$\begin{array}{cc} R_1 & O \\ | & || \\ >C-(CH_2)_n-CR_2, & \end{array}$        $\begin{array}{cc} R_1 & O \\ | & || \\ >C-(CH_2)_n-C-OR_2, & \end{array}$

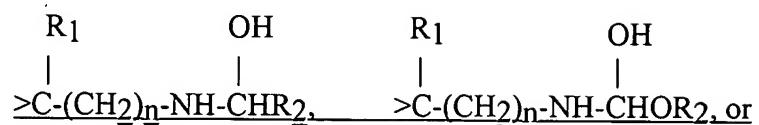
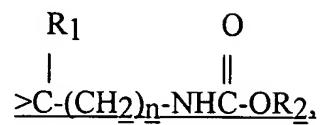
$\begin{array}{cc} R_1 & OH \\ | & | \\ >C-(CH_2)_n-CHR_2, & \end{array}$        $\begin{array}{cc} R_1 & OH \\ | & | \\ >C-(CH_2)_n-CH-OR_2, & \end{array}$

$\begin{array}{cc} R_1 & O \\ | & || \\ >C-NH(CH_2)_n-CR_2, & \end{array}$        $\begin{array}{cc} R_1 & OH \\ | & | \\ >C-NH(CH_2)_n-CHR_2, & \end{array}$

$\begin{array}{cc} R_1 & OH \\ | & | \\ >C-NH(CH_2)_n-CH-OR_2, & \end{array}$

$\begin{array}{cc} R_1 & O \\ | & || \\ >C-NH(CH_2)_n-C-OR_2, & \end{array}$        $\begin{array}{cc} R_1 \\ | \\ >C-NH(CH_2)_n-OR_2, \end{array}$

$\begin{array}{cc} R_1 \\ | \\ >C-NH(CH_2)_n-R_2, \end{array}$        $\begin{array}{cc} R_1 & O \\ | & || \\ >C(CH_2)_n-NHCR_2, & \end{array}$



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$\begin{array}{c} R_1 \\ | \\ >C-(CH_2)_n-NH-CH_2OR_2, \text{ where } n \text{ is } 0-6; \end{array}$

or

B)  $Z''$  is  $-Y-CH-$  or  $-CH-Y-$  where  $R_p$

$\begin{array}{c} | \quad | \\ R_p \quad R_p \end{array}$

is  $-R_1, OR_1, -SR_1, -F, -NHR_2, -Br$  or  $-I$  and  $Y$  is defined as in III(A);

and

IV. provided that when each  $R_b, R_c, R_d, R_e, R_i, R_j, R_k, R_L, R_m$  and  $R_o$  is H;

$R_f$  is  $-CH_3$ ;

$R_g$  is  $-OH$ ;

$Z'$  is  $>COH$ ; and

$Z''$  is  $>CH_2$ ;

then  $R_a$  is not  $-H$ ;

where, in each formula set forth above, each  $R_1$  and  $R_2$  independently is  $-H$ , or a substituted or unsubstituted alkyl, alkenyl or alkynyl group of up to 6 carbons. Those skilled in the art will appreciate that the invention extends to other compounds within the formulae given in the claims below, having the described characteristics. These characteristics can be determined for each test compound using the assays detailed below and elsewhere in the literature.

Please rewrite page 4, paragraph 4, as follows:

Without wishing to bind myself to specific mechanisms or theory, it appears that certain compounds that are known to inhibit microtubule formation, bind tubulin and exhibit anti-mitotic properties such as colchicine and combretastatin A-4 share certain structural similarities with estradiol. Fig. 3 illustrates the molecular formulae of estradiol, colchicine,

combreastatin A-4, and improved estradiol derivatives that bind tubulin, inhibit microtubule assembly and exhibit anti-mitotic properties. Molecular formulae are drawn and oriented to emphasize structural similarities between the ring structures of colchicine, combreastatin A-4, estradiol, and certain estradiol derivatives. Estradiol derivatives are made by incorporating colchicine or combreastatin A-4 structural motifs into the steroid backbone of estradiol.

Page 5, please insert immediately before the line which reads "Anti-mitotic Activity *In Situ*" the following new header:

#### DETAILED DESCRIPTION OF THE INVENTION

Please rewrite page 10, last paragraph, as follows:

It should be understood that in addition to the ingredients, particularly mentioned above, the formulations of this invention may include other agents [convention] conventional in the art having regard to the type of formulation in question, for example, those suitable for oral administration may include flavoring agents.

#### Amendments in the Claims:

In accordance with 37 CFR 1.121(c), the following versions of the claims as rewritten by the foregoing amendment show all the changes made relative to the previous versions of the claims.

Claims 1-40 have been cancelled.

Claims 41-46 have been added.

REMARKS

Prior to examination of the above-referenced application, applicants respectfully request entry of the amendments as indicated above.

The present application is a continuation of U.S. Application Serial No. 09/243,158 filed February 2, 1999, which is a divisional of U.S. Application Serial No. 08/838,699 filed April 25, 1997, now U.S. Patent No. 5,892,069, which is a divisional of U.S. Application Serial No. 08/571,265 filed December 12, 1995, now U.S. Patent No. 5,661,143, which is a continuation of Application No. 08/102,767, filed August 6, 1993, now U.S. Patent No. 5,504,074. This application is also a continuation of 09/780,650, filed February 12, 2001, which is a continuation of 09/436,610, filed November 9, 1999, abandoned, which is also a continuation of 09/243,158, filed February 2, 1999.

Support for the new claims can be found in the specification and claims as originally filed. Support for the addition of the compound on page 4, third paragraph, is found in original Claim 1. Applicants believe that the claims are in condition for allowance. A Notice of Allowance is therefore respectfully solicited. If the Examiner believes any informalities remain in the application that may be corrected by Examiner's Amendment, or there are any other issues that can be resolved by telephone interview, a telephone call to the undersigned attorney at (404) 745-2408 is respectfully solicited.

Respectfully submitted,

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